
Tumor necrosis factor overcomes immune evasion in p53-mutant medulloblastoma.

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Authors: Alexandra Garancher, Hiromichi Suzuki, Svasti Haricharan, Lianne Q Chau, Meher Beigi Masihi, Jessica M Rusert, Paula S Norris, Florent Carrette, Megan M Romero, Sorana A Morrissy, Patryk Skowron, Florence M G Cavalli, Hamza Farooq, Vijay Ramaswamy, Steven J M Jones, Richard A Moore, Andrew J Mungall, Yussanne Ma, Nina Thiessen, Yisu Li, Alaide Morcavallo, Lin Qi, Mari Kogiso, Yuchen Du, Patricia Baxter, Jacob J Henderson, John R Crawford, Michael L Levy, James M Olson, Yoon-Jae Cho, Aniruddha J Deshpande, Xiao-Nan Li, Louis Chesler, Marco A Marra, Harald Wajant, Oren J Becher, Linda M Bradley, Carl F Ware, Michael D Taylor, Robert J Wechsler-Reya

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Public Summary:

Many immunotherapies act by enhancing the ability of cytotoxic T cells to kill tumor cells. Killing depends on T cell recognition of antigens presented by class I major histocompatibility complex (MHC-I) proteins on tumor cells. In this study, we showed that medulloblastomas lacking the p53 tumor suppressor do not express surface MHC-I and are therefore resistant to immune rejection. Mechanistically, this is because p53 regulates expression of the peptide transporter Tap1 and the aminopeptidase Erp1, which are required for MHC-I trafficking to the cell surface. In vitro, tumor necrosis factor (TNF) or lymphotoxin-beta receptor agonist can rescue expression of Erp1, Tap1 and MHC-I on p53-mutant tumor cells. In vivo, low doses of TNF prolong survival and synergize with immune checkpoint inhibitors to promote tumor rejection. These studies identified p53 as a key regulator of immune evasion and suggest that TNF could be used to enhance sensitivity of tumors to immunotherapy.

Scientific Abstract:

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